Aminomethylation of Enals through Carbene and Acid Cooperative Catalysis: Concise Access to β²-Amino Acids**

Jianfeng Xu, Xingkuan Chen, Ming Wang, Pengcheng Zheng, Bao-An Song, and Yonggui Robin Chi*

Abstract: A convergent, organocatalytic asymmetric aminomethylation of α,β -unsaturated aldehydes by N-heterocyclic carbene (NHC) and (in situ generated) Brønsted acid cooperative catalysis is disclosed. The catalytically generated conjugated acid from the base plays dual roles in promoting the formation of azolium enolate intermediate, formaldehydederived iminium ion (as an electrophilic reactant), and methanol (as a nucleophilic reactant). This redox-neutral strategy is suitable for the scalable synthesis of enantiomerically enriched β^2 -amino acids bearing various substituents.

*B***-A**mino acids are important building blocks for bioactive molecules^[1] and designed peptidic foldamers^[2] exhibiting well-defined secondary structures with increased stability towards protease degradation. Considerable efforts have been made toward the development of novel strategies for the effective synthesis of enantiopure β -amino acids.^[3] β^3 -Amino acids (those with substituents at the β -position) are now commercially available with most natural substituents.^[4] In contrast, the analogous β^2 -amino acids (those with substituents at the α -position), although equally useful and wildly existed in natural products and pharmaceuticals,^[5] are far less accessible (Figure 1 a).^[6] Most of the reported methods for β^2 -amino acids employ chiral auxiliaries to control the stereochemistry.^[7] The catalytic asymmetric approaches to construct β^2 -amino acids and their derivatives are limited.^[8] In the arena of organocatalysis, Gellman and coworkers developed a chiral secondary-amine-catalyzed Man-

[*] Dr. J. Xu,^[+] X. Chen,^[+] Dr. M. Wang, P. Zheng, Prof. Dr. Y. R. Chi Division of Chemistry & Biological Chemistry, School of Physical & Mathematical Sciences, Nanyang Technological University Singapore 637371 (Singapore) E-mail: robinchi@ntu.edu.sg

P. Zheng, B.-A. Song, Prof. Dr. Y. R. Chi Laboratory Breeding Base of Green Pesticide and Agricultural Bioengineering, Key Laboratory of Green Pesticide and Agricultural Bioengineering, Ministry of Education, Guizhou University Huaxi District, Guiyang 550025 (China)

- [⁺] These authors contributed equally to this work.
- [**] We acknowledge financial support from the Singapore National Research Foundation, the Ministry of Education of Singapore, Nanyang Technological University (NTU, Singapore), China's National Key program for Basic Research (No. 2010CB126105), "Thousand Talent Plan", National Natural Science Foundation of China (No. 21132003; No. 21472028), Guizhou Province Returned Oversea Student Science and Technology Activity Program, and Guizhou University (China).
 - Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/anie.201412132.



Figure 1. β^2 -Amino acids and our synthetic strategy.

nich reaction to prepare β^2 -amino aldehydes as a key step for β^2 -amino acid synthesis.^[8d,e] List and co-workers described a catalytic asymmetric thiourea-mediated transfer hydrogenation reaction to form β^2 -nitroesters which can be further converted into β^2 -amino acids.^[8f] Despite the progress, the development of a convergent, enantioselective, and practical route for the scalable preparation of β^2 -amino acids with various substitution patterns is still in urgent need.

Herein we disclose a concise and scalable asymmetric organocatalytic approach for practical access to β^2 -amino acids and their derivatives (Figure 1 b). Our reaction involves the simultaneous dual activation of two substrates (an α,β -unsaturated aldehyde/enal^[9] and an N,O-acetal) by two organic catalysts [an N-heterocyclic carbene (NHC)^[10] and an in situ generated Brønsted acid]. The key catalytic step results in an α -carbon aminomethylation of the enal by an internal redox process to produce β^2 -amino esters, which can be readily converted into properly protected β^2 -amino esters in a one-pot operation (Figure 1b). This study should encourage further exploration on using the in situ generated conjugated acid from NHC chemistry for catalysis design and reaction development. On the practical side, the simplicity of our method should benefit the chemistry, chemical biology,

Angew. Chem. Int. Ed. 2015, 54, 1-6

© 2015 Wiley-VCH Verlag GmbH & Co. KGaA, Weinheim

Wiley Online Library

and material communities where enantiomerically enriched β^2 -amino acids are used. Notably, the synthesis of β^3 -amino acids from α -aryloxyacetaldehydes and aryl-aldehyde-derived imines by NHC catalysis has been previously reported by Scheidt and co-workers.^[11]

Our reaction design is further illustrated in Figure 1 c. The deprotonation of the NHC pre-catalyst (NHC·HX) by base can lead to two new catalysts, a free NHC (I) and a Brønsted acid (base·HX; catalyst II). Under the co-activation of I and II, the enal substrate 1 turns into an azolium enolate intermediate (III), as previously reported by Bode and coworkers^[12a,b] and our group.^[12c] Concurrently, promoted by acid catalyst II, the N,O-acetal substrate 2^[13] splits into the formaldehyde-derived iminium ion IV and methanol. The iminium ion IV behaves as an electrophilic substrate to undergo a Mannich reaction with III, followed by trapping of the resulting acyl azolium with the methanol molecule, which was generated in the previous step, to release the NHC catalyst and form the β^2 -amino ester in high optical purity.^[14] A more complete pathway is detailed in the Supporting Information.

Notably, the combined use of NHC and either Lewis or Brønsted acid catalysts have recently been described by the groups of Scheidt,^[15] Rovis,^[16] You,^[17] Xu,^[18] Snyder,^[19] Yao,^[20] as well as our own group.^[21] In the previous studies, the acid cocatalysts were used to improve the reaction yields or selectivities. In particular, Rovis and co-workers reported an enal homoenolate addition to α,β -unsaturated imines promoted by an insitu generated acid cocatalyst.^[16] In our present study, the in situ generated Brønsted-acid co-catalyst plays two critical roles: one is to switch the regioselectivity of the enal substrate by forming III (Figure 1 c) through protonation of the β -carbon atom of the homoenolate intermediate (see the Supporting Information).^[12] The other is to catalyze the formation of the formaldehyde-derived iminium ion (as an electrophilic reactant) and methanol (as a nucleophilic reactant) from the N,O-acetal substrate. Imines are important nitrogen sources in organic synthesis.^[22] However, imines (or iminiums) derived from formaldehvde are challenging substrates in asymmetric catalytic reactions because of the high reactivities and thus difficult to control both the chemo- and stereoselectivities.^[23] Our approach offers mild, weakly acidic conditions which allow controlled in situ generation of a formaldehyde-derived iminium from its N,O-acetal precursor for highly chemo- and enantioselecitve reactions.

Key results of our initial reaction optimization are summarized in Table 1. The enal **1a** and N,O-acetal **2** were chosen as the model substrates to test the feasibility of this proposed cooperative catalysis strategy. To our delight, when the aminoindanol-derived triazolium salt **A**^[12a] was used as an NHC precatalyst and NaOAc was used as a base, the desired β^2 -amino ester **3a** was isolated in 61 % yield and 95:5 e.r. (Table 1, entry 1). Replacing **A** with the triazolium salt **B**^[24a] resulted in a decrease in yield and e.r. value (entry 2). The phenylalanine-derived precatalyst **C**^[24b] could also mediate the reaction but with less satisfactory results (entry 3). We then chose **A**, first developed by Bode and co-workers, for further optimization of the reaction conditions. The use of a strong organic base (DBU) led to nearly no product *Table 1:* Condition optimization.^[a]



[a] Reaction conditions unless otherwise specified: **1a** (0.2 mmol), **2** (0.1 mmol), NHC (0.02 mmol), base (0.02 mmol), CH_2Cl_2 (1 mL), RT, 24 h. [b] Yield of isolated product based on **2**. [c] Enantiomeric ratio of **3a**, determined by chiral-phase HPLC analysis. The absolute configuration of the major enantiomer was assigned by comparison with the literature (see the Supporting Information). [d] 0.15 mmol of **1a** was used. [e] 0.1 mmol of **1a** was used. DBU = 1,8-diazabicycloundec-7-ene, DIPEA = *N*,*N*-diisopropylethylamine, DMAP = 4-timethylaminopyridine, Mes = 2,4,6-trimethylphenyl, n.d. = not determined.

formation, likely because DBU was not a suitable base to promote the azolium enolate intermediate formation (entry 4).^[12a,b] Weaker organic bases such as DIPEA, Et₃N, and DMAP could effectively mediate this reaction, with Et₃N giving the best result in 77% yield and 95:5 e.r. (entries 5–7). An inorganic base such as K₂CO₃ was also compatible with this reaction, albeit furnishing the product in a lower yield (entry 8). We next found that slightly raising the reaction temperature to 40 °C could afford a cleaner reaction mixture (with less side product 3a' formed; entries 9 versus 6) which was easier to handle technically, during product purification, without sacrificing the product yield and e.r. value. The reaction did not proceed without the addition of an external base (entry 10). It appeared that the N,O-acetal substrate itself is not a sufficient base. Decreasing the amount of the enal substrate led to slightly lower yields (entries 11 and 12). A major side reaction was self-redox conversion of 1a into the hydrocinnamic acid methyl ester 3a'.^[25]

With the optimal reaction conditions in hand (Table 1, entry 9), we first established the generality of this reaction. As shown in Table 2, a board range of enals exhibiting diverse electronic and steric properties were explored.^[26] The use of cinnamaldehyde (**1a**) afforded the desired product **3a** in 76% yield and 95:5 e.r. Enals with electron-donating (4-Me and 4-OMe) or electron-withdrawing groups (4-F, 4-Cl, and 4-Br)

www.angewandte.org

© 2015 Wiley-VCH Verlag GmbH & Co. KGaA, Weinheim



[a] Reaction conditions unless otherwise specified: 1 (0.2 mmol), 2 (0.1 mmol), NHC A (0.02 mmol), Et_3N (0.02 mmol), CH_2Cl_2 (1 mL), 40 °C, 24 h. [b] 0.5 mmol of enal was used.

on their β -phenyl ring led to the corresponding β^2 -amino esters 3b-f in good yields and high enantioselectivities. Switching the bromo substituent from the para- to either meta- or ortho-position had little impact on the reaction yields or enantioselectivities (3 f-h). Enals containing easily transformable functional groups such as 4-NO₂, 4-COOMe, and 4-CHO were well tolerated, thus providing the corresponding products 3i-k in moderate to good yields and high enantioselectivities. When an aldehyde moiety (4-CHO) was placed on the β -phenyl ring (3k), the reaction exclusively proceeded through the enolate pathway, that is, no benzoin or azabenzoin products were observed. Our present synthesis provides a complementary approach to earlier methods developed by the groups of Gellman^[8d,e] and List.^[8f] Notably, our method can tolerate functional groups such as NO_2 (3i) and CHO (3k) which are not compatible with the Gellman and List reaction conditions. Enals with sterically demanding substituents such as 1-naphthyl and 2-naphthyl reacted effectively as well (31 and 3m). Heteoaryl-substituted enals can be readily accommodated, thus achieving the corresponding 2-furyl, 2-thienyl, and 3-pyridinyl-substituted products **3n-p** in good yields and high enantioselectivities. The use of enals with an ester or alkyl substituent on the β -carbon atom also led to desired products (3q and 3r), albeit with lower yields. The β -ester-substituted β^2 -amino ester **3q** could be further converted into synthetically useful β-proline.^[27] The drop in yield of the aliphatic product **3r** was attributed to the fast decomposition of the iminium ion into dibenzylamine, which consumed **2** and caused additional reactions^[28] of the β -alkyl enal substrate. For example, when β -alkyl enal (for **3r**) was used, around 52% of **2** was decomposed into dibenzylamine at the end of the reaction, as indicated by ¹H NMR analysis of the crude reaction mixture. In the case of the β -aryl enal reaction (e.g., for **3a**), only around 13% of **2** was observed to be decomposed to dibenzylamine.

A major limitation of most synthetic routes to β^2 -amino acids is the difficulty in introducing acid- or base-sensitive functional groups. Our method does not require strong acid or base conditions, thus making it well-suited for the synthesis of β^2 -amino acids bearing side-chain functionality. To validate this utility, we next set out to synthesize β^2 -amino esters with natural substituents by employing *ent*-**A** as an NHC precatalyst, as illustrated in Table 3. The use of β -aryl/heteroarylsubstituted enals afforded β^2 -homophenylalanine, homotyr-

Table 3: Synthesis of $\beta^2\text{-amino esters bearing aromatic and aliphatic natural substituents. <math display="inline">^{[a]}$



[a] Reaction conditions unless otherwise specified: **1** (0.2 mmol), 2 (0.1 mmol), NHC *ent*-**A** (0.02 mmol), Et₃N (0.02 mmol), CH₂Cl₂ (1 mL), 40 °C, 24 h. [b] 0.5 mmol of enal was used. Boc = *tert*-butoxycarbonyl, MOM = methoxycarbonyl.

osine, and homotryptophan esters (**4a**–c) in good yields and high enantioselectivities. When β -alkyl-substituted enals were used, the corresponding β^2 -homoleucine, homomethionine esters **4d** and **4e** were successfully obtained, albeit in moderate yields. Functionalities such as esters and amides on the β -carbon atom of the enal were well tolerated, thus furnishing β^2 -homoaspartic acid, and the homoasparagine esters **4f** and **4g** in moderate yields and moderate to good enantioselectivities.

The catalytic reaction products could be readily converted into properly protected β^2 -amino acids or esters. For example, the β^2 -amino ester **3a** was transformed into the N-protected *ent*- β^2 -homophenylalanine **6** by simple and scalable operations (Scheme 1). It is worth noting that the aminomethyla-

www.angewandte.org

Angewandte Communications



Scheme 1. Concise synthesis of N-protected β^2 -homophenylalanine.

tion, debenzylation, and Boc protection steps could be combined in a one-pot operation, thus affording the β^2 -amino ester **5** in 59% overall yield and 95:5 e.r. Such an operation is very appealing to large-scale synthesis since only one separation step is required. The β^2 -amino ester **5** could be readily converted into either the Boc- or Fmoc-protected *ent*- β^2 -homophenylalanine (**6a** or **6b**) through simple transformations.

In summary, we have developed an NHC and Brønsted acid cocatalyzed aminomethylation of α , β -unsaturated aldehydes to afford β^2 -amino esters in good yields and high enantioselectivities. The catalytically generated conjugated acid cocatalyst plays dual roles in promoting generation of the azolium enolate intermediate and formation of the formal-dehyde-derived iminium ion. The reaction conditions are mild and various functional groups can be tolerated: seven β^2 -amino esters with natural substituents were successfully synthesized using this protocol. These β^2 -amino esters can be easily converted into the corresponding N-protected β^2 -amino acids by simple operations.

Received: December 18, 2014 Revised: February 9, 2015 Published online:

Keywords: amino acids · asymmetric synthesis · Brønsted acid · N-heterocyclic carbenes · organocatalysis

- a) P. R. Cheng, S. H. Gellman, W. F. DeGrado, *Chem. Rev.* 2001, 101, 3219; b) D. Seebach, A. K. Beck, D. J. Bierbaum, *Chem. Biodiversity* 2004, 1, 1111.
- [2] a) D. H. Appella, L. A. Christianson, I. L. Karle, D. R. Powell, S. H. Gellman, J. Am. Chem. Soc. 1996, 118, 13071; b) D. H. Appella, L. A. Christianson, D. Klein, D. R. Powell, X. Huang, J. J. Barchi, S. H. Gellman, Nature 1997, 387, 381; c) E. A. Porter, X. Wang, H.-S. Lee, B. Weisblum, S. H. Gellman, Nature 2000, 404, 565; d) J. Frackenpohl, P. I. Arvidsson, J. V. Schreiber, D. Seebach, ChemBioChem 2001, 2, 445; e) H. Wiegand, B. Wirz, A. Schweitzer, G. P. Camenisch, M. I. Rodriguez Perez, G. Gross, R. Woessner, R. Voges, P. I. Arvidsson, J. Frackenpohl, D. Seebach, Biopharm. Drug Dispos 2002, 23, 251; f) S. Sagan, T. Milcent, R. Ponsinet, O. Convert, O. Tasseau, G. Chassaing, S. Lavielle, O. Lequin, Eur. J. Biochem. 2003, 270, 939; g) S. J. Miller, Acc. Chem. Res. 2004, 37, 601; h) J. T. Blank, S. J. Miller, Biopolymers 2006, 84, 38; i) R. S. Erdmann, H. Wennemers, J. Am. Chem. Soc. 2010, 132, 13957.
- [3] Enantioselective Synthesis of β-Amino Acids, 2nd ed. (Eds.: E. Juaristi, V. A. Soloshonok), Wiley-VCH, Weinheim, 2005.
- [4] For a review on the synthesis of β³-amino acids, see: H. J. Drexler, J. You, S. Zhang, C. Fisher, W. Baumann, A. Spannenberg, D. Heller, *Org. Process Res. Dev.* 2003, 7, 355.

- [5] a) β-Amino Acids in Nature: F. V. Nussbaum, P. Spiteller, in *Highlights in Bioorganic Chemistry*, (Eds.: C. Schmuck, H. Wennemers), Wiley-VCH, Weinheim, **2003**, p. 63; b) Biosynthesis of β-Amino Acids: P. Spiteller, F. V. Nussbaum, in *Highlights in Bioorganic Chemistry*, (Eds.: C. Schmuck, H. Wennemers), Wiley-VCH, Weinheim, **2003**; p. 90.
- [6] For a review on the chemistry of β²-amino acids, see: G. Lelais, D. Seebach, *Biopolymers* 2004, 76, 206.
- [7] a) J. E. Beddow, S. G. Davies, A. D. Smith, A. J. Russell, *Chem. Commun.* 2004, 2778; b) A. Tessier, N. Lahmar, J. Pytkowicz, T. Brigaud, *J. Org. Chem.* 2008, *73*, 3970.
- [8] a) H. M. L. Davies, C. Venkataramani, Angew. Chem. Int. Ed. 2002, 41, 2197; Angew. Chem. 2002, 114, 2301; b) A. Duursma, A. J. Minnaard, B. L. Feringa, J. Am. Chem. Soc. 2003, 125, 3700; c) M. P. Sibi, K. Patil, Angew. Chem. Int. Ed. 2004, 43, 1235; Angew. Chem. 2004, 116, 1255; d) Y. Chi, S. H. Gellman, J. Am. Chem. Soc. 2006, 128, 6804; e) Y. Chi, E. P. English, W. C. Pomerantz, W. S. Horne, L. A. Joyce, L. R. Alexander, W. S. Fleming, E. A. Hopkins, S. H. Gellman, J. Am. Chem. Soc. 2007, 129, 6050; f) N. J. A. Martin, X. Cheng, B. List, J. Am. Chem. Soc. 2008, 130, 13862.
- [9] Our attempts in using carboxylic esters as the enolate precursors were unsuccessful. In our earlier ester strategy, strong base is normally required for the generation of the enolate intermediate. The strong basic conditions are not compatible with the present reaction as the generation of iminium ion from the N,Oacetal (Figure 1 c) requires weakly acidic conditions. For relevant references, see: a) L. Hao, Y. Du, H. Lv, X. Chen, H. Jiang, Y. Shao, Y. R. Chi, Org. Lett. 2012, 14, 2154; b) L. Hao, S. Chen, J. Xu, B. Tiwari, Z. Fu, T. Li, J. Lim, Y. R. Chi, Org. Lett. 2013, 15, 4956; c) S. Chen, L. Hao, Y. Zhang, B. Tiwari, Y. R. Chi, Org. Lett. 2013, 15, 5822; d) Z. Q. Fu, J. F. Xu, T. S. Zhu, W. W. Y. Leong, Y. R. Chi, Nat. Chem. 2013, 5, 835; e) J. Xu, Z. Jin, Y. R. Chi, Org. Lett. 2013, 15, 5028.
- [10] For selected recent reviews on NHC catalysis, see: a) D. Enders, O. Niemeier, A. Henseler, Chem. Rev. 2007, 107, 5606; b) N. Marion, S. Díez-González, S. P. Nolan, Angew. Chem. Int. Ed. 2007, 46, 2988; Angew. Chem. 2007, 119, 3046; c) V. Nair, R. S. Menon, A. T. Biju, C. R. Sinu, R. Paul, A. Jose, V. Sreekumar, Chem. Soc. Rev. 2011, 40, 5336; d) Z. Q. Rong, W. Zhang, G. Q. Yang, S.-L. You, Curr. Org. Chem. 2011, 15, 3077; e) H. U. Vora, T. Rovis, Aldrichimica Acta 2011, 44, 3; f) D. T. Cohen, K. A. Scheidt, Chem. Sci. 2012, 3, 53; g) J. Douglas, G. Churchill, A. D. Smith, Synthesis 2012, 44, 2295; h) X.-Y. Chen, S. Ye, Synlett 2013, 24, 1614; i) S. J. Ryan, L. Candish, D. W. Lupton, Chem. Soc. Rev. 2013, 42, 4906; j) S. De Sarkar, A. Biswas, R. C. Samanta, A. Studer, Chem. Eur. J. 2013, 19, 4664; k) J. Mahatthananchai, J. W. Bode, Acc. Chem. Res. 2014, 47, 696; 1) M. N. Hopkinson, C. Richter, M. Schedler, F. Glorius, Nature 2014, 510, 485; m) S. J. Connon, Angew. Chem. Int. Ed. 2014, 53, 1203: Angew. Chem. 2014, 126, 1225.
- [11] Y. Kawanaka, E. M. Phillips, K. A. Scheidt, J. Am. Chem. Soc. 2009, 131, 18028.
- [12] a) M. He, J. R. Struble, J. W. Bode, J. Am. Chem. Soc. 2006, 128, 8418; b) J. Kaeobamrung, M. C. Kozlowski, J. W. Bode, Proc. Natl. Acad. Sci. USA 2010, 107, 20661; c) Z. Fu, H. Sun, S. Chen, B. Tiwari, G. Li, Y. R. Chi, Chem. Commun. 2013, 49, 261; d) Y.-M. Zhao, M. S. Cheung, Z. Lin, J. Sun, Angew. Chem. Int. Ed. 2012, 51, 10359; Angew. Chem. 2012, 124, 10505.
- [13] D. Enders, D. Ward, J. Adam, G. Raabe, Angew. Chem. Int. Ed. Engl. 1996, 35, 981; Angew. Chem. 1996, 108, 1059.
- [14] Attempts to directly form peptides by trapping the acyl azolium intermediate VI (see Scheme S1 in the Supporting Information) with an external amino ester were not successful. When primary amino ester (phenylalanine ester) was added to the reaction mixture, 3a was nearly undetectable.

www.angewandte.org

© 2015 Wiley-VCH Verlag GmbH & Co. KGaA, Weinheim

Angew. Chem. Int. Ed. 2015, 54, 1-6



- [15] a) D. E. A. Raup, B. Cardinal-David, D. Holte, K. A. Scheidt, *Nat. Chem.* 2010, *2*, 766; b) B. Cardinal-David, D. E. A. Raup, K. A. Scheidt, *J. Am. Chem. Soc.* 2010, *132*, 5345; c) E. M. Phillips, M. Riedrich, K. A. Scheidt, *J. Am. Chem. Soc.* 2010, *132*, 13179; d) D. T. Cohen, B. Cardinal-David, K. A. Scheidt, *Angew. Chem. Int. Ed.* 2011, *50*, 1678; *Angew. Chem.* 2011, *123*, 1716; e) J. Dugal-Tessier, E. A. O'Bryan, T. B. H. Schroeder, D. T. Cohen, K. A. Scheidt, *Angew. Chem. Int. Ed.* 2012, *51*, 4963; *Angew. Chem.* 2012, *124*, 5047; f) E. O. McCusker, K. A. Scheidt, *Angew. Chem. Int. Ed.* 2013, *52*, 13616; *Angew. Chem.* 2013, *125*, 13861.
- [16] X. D. Zhao, D. A. DiRocco, T. Rovis, J. Am. Chem. Soc. 2011, 133, 12466.
- [17] Z.-Q. Rong, M.-Q. Jia, S.-L. You, Org. Lett. 2011, 13, 4080.
- [18] G. Liu, P. D. Wilkerson, C. A. Toth, H. Xu, Org. Lett. 2012, 14, 858.
- [19] A. M. ElSohly, D. A. Wespe, T. J. Poore, S. A. Snyder, Angew. Chem. Int. Ed. 2013, 52, 5789; Angew. Chem. 2013, 125, 5901.
- [20] Z. Xiao, C. Yu, T. Li, X. Wang, C. Yao, Org. Lett. 2014, 16, 3632.
- [21] J. Mo, X. Chen, Y. R. Chi, J. Am. Chem. Soc. 2012, 134, 8810.
- [22] a) M. He, J. W. Bode, J. Am. Chem. Soc. 2008, 130, 418; b) M. Rommel, T. Fukuzumi, J. W. Bode, J. Am. Chem. Soc. 2008, 130, 17266; c) D. A. DiRocco, T. Rovis, Angew. Chem. Int. Ed. 2012, 51, 5904; Angew. Chem. 2012, 124, 6006; d) H. Lv, B. Tiwari, J. Mo, C. Xing, Y. R. Chi, Org. Lett. 2012, 14, 5412; e) L.-H. Sun,

Z.-Q. Liang, W.-Q. Jia, S. Ye, Angew. Chem. Int. Ed. 2013, 52, 5803; Angew. Chem. 2013, 125, 5915; f) J. Xu, C. Mo, T. Zhu, B.-A. Song, Y. R. Chi, Org. Lett. 2014, 16, 3272.

- [23] I. Ibrahem, J. Casús, A. Córdova, Angew. Chem. Int. Ed. 2004, 43, 6528; Angew. Chem. 2004, 116, 6690.
- [24] a) I. Piel, M. Steinmetz, K. Hirano, R. Fröhlich, S. Grimme, F. Glorius, *Angew. Chem. Int. Ed.* 2011, *50*, 4983; *Angew. Chem.* 2011, *123*, 5087; b) P.-C. Chiang, M. Rommel, J. W. Bode, *J. Am. Chem. Soc.* 2009, *131*, 8714. For a general method that used for the preparation of a NHC precatalyst, see: c) M. S. Kerr, J. Read deAlaniz, T. Rovis, *J. Org. Chem.* 2005, *70*, 5725.
- [25] For selected examples, see: a) A. Chan, K. A. Scheidt, *Org. Lett.* **2005**, 7, 905; b) S. S. Sohn, J. W. Bode, *Org. Lett.* **2005**, 7, 3873;
 c) K. Zeitler, *Org. Lett.* **2006**, *8*, 637.
- [26] α-Substituted enal is not a suitable substrate for this reaction. Iminiums derived from secondary amines and substituted aldehyde or ketone are challenging to prepare.
- [27] a) C. Mazzini, J. Lebreton, V. Alphand, R. Furstoss, J. Org. Chem. **1997**, 62, 5215; b) J. Blanchet, M. Pouliquen, M.-C. Lasne, J. Rouden, *Tetrahedron Lett.* **2007**, 48, 5727.
- [28] For possible dibenzylamine catalyzed β-alkyl enal side reactions such as dienamine catalysis, see: a) D. B. Ramachary, Y. V. Reddy, *Eur. J. Org. Chem.* **2012**, *5*, 865; b) H. Jiang, L. Albrecht, K. A. Jørgensen, *Chem. Sci.* **2013**, *4*, 2287.



Communications

Organocatalysis

J. Xu, X. Chen, M. Wang, P. Zheng, B.-A. Song, Y. R. Chi* _____ **IIII**-IIII

Aminomethylation of Enals through Carbene and Acid Cooperative Catalysis: Concise Access to β^2 -Amino Acids



Harmonious cooperation: An N-heterocyclic carbene (NHC) and (in situ generated) Brønsted acid cooperatively catalyze the aminomethylation of α , β -unsaturated aldehydes. This cooperative catalytic reaction provides a redox neutral strategy for quick access to β^2 -amino esters in an enantioselective manner.

6 www.angewandte.org

© 2015 Wiley-VCH Verlag GmbH & Co. KGaA, Weinheim

Angew. Chem. Int. Ed. 2015, 54, 1-6